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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/678,953	10/03/2000	Hiroshi Kubota	320727.50401.	7343

7590 03/08/2005

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

HL

Office Action Summary	Application No.	Applicant(s)	
	09/678,953	KUBOTA ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,14 and 27-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 14, 27-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/10/05 has been entered.

Applicants' Amendment and Response has been entered and considered. Claims 2-13 and 15-26 have been cancelled. Claims 1, 14 have been amended. Claims 27-55 have been added. Claims 1, 14 and 27-55 are pending and under current examination.

Response to Arguments

The prior rejection of claims 1-20, under 112, 2nd ¶, as being indefinite because the claims previously recite, "a composition comprising isolated single-cell bipotent hepatic progenitors" is withdrawn in view of Applicants' amendment to the claims 1 and 14, which now recite, "A isolated single cell bipotent hepatic progenitor" and "A composition consisting essentially of isolated single-cell bipotent hepatic progenitors", respectively. This obviates the prior rejection because these recitations do not encompass single bipotent hepatic progenitor cells present in a whole liver. See p. 8 of the Response.

The prior rejection of claims 1-20 as being anticipated by Sargiacomo is found to be overcome in part. In particular, the claims as instantly presented, overcome the prior rejection, with regard to the breadth of the claims, which recite bipotent hepatic progenitors are no longer anticipated by Sargiacomo because ethey do not teach isolated, single cell bipotent hepatic progenitors. However, certain of the claims (14, 28, 42-49) recite progeny of the bipotent hepatic progenitor cells. This embodiment of the claims is anticipated by Sargiacomo, because the progeny of progenitor cells includes, for example, further differentiated hepatic cells, such as hepatocytes.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 14, 27-55 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-

20 of copending Application No. 10/358,325. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to bipotent hepatic progenitor cells. The instant claims are directed to isolated single-cell bipotent hepatic progenitor cells, the '325 claims are directed to compositions comprising bipotent hepatic progenitor cells. Both sets of claims recite the same markers to characterize the claimed cells. Thus, the instant claims are obvious over the '325 claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 14, 27-55 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-30, 33, 27-30, 33, 35-46, 53-60 of copending Application No. 10/135,700. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '700 application require the compositions of the instantly claimed application. The instant claims are directed to isolated single cell bipotent hepatic progenitor cells. The '700 claims are directed to methods of propagating the hepatic progenitor cells, methods of identifying hepatic differentiation/growth factors/hepatic toxins, developing drugs/identifying novel antimicrobials using the claimed progenitor cells. Thus, because the '700 claims recited methods of propagating the instantly claimed hepatic progenitor cells, they

are rendered obvious. Note that the '700 claims provide the same characteristics as the instant claims to identify the hepatic progenitor cells. Furthermore, this rejection is found to be proper, because the claims of propagating the hepatic progenitor cells were not provided in the instant case for restriction purposes.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 14, 27-55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors

have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention. The claimed invention is directed to isolated, single-cell bipotent hepatic progenitor cells which express at least one intercellular adhesion molecule (ICAM) antigen, does not express major histocompatibilitiy complex (MHC) class Ia antigen, express at least one MHC class 1b antigen, exhibit numerically higher sidescatter value determined by flow cytometry than the side scatter value of nonparenchymal cell sof the same species, express alpha-fetoprotein, albumin, CK19, or combinations thereof, and the progenitor cells are capable of differentiation with exposed to differentiation-inducing conditions.

Breadth of the claims. The claims are broad. The recitation of the expression of particular markers, and the lack of expression of other markers fails to provide specific guidance to arrive at the claimed invention.

Guidance of the Specification/The Existence of Working Examples. The specification teaches the establishment of hepatic cell lines from fetal rat livers. See 6.1, p. 14. Further, the specification teaches that the cells are then analyzed by flow cytometry. See p. 16. In particular, the specification teaches the identification of hepatic progenitor cells from the fetal liver cell lines. The specification teaches that in order to identify the hepatic progenitor cells, surface antigenic markers and colony forming assays were used. See p. 20, #6.4. The specification particularly teaches that when compared to an adult hepatocarcinoma cell line (FTO-2B), these

cells have no expression of MHC class I, dull expression of MHC class Ib and positive for ICAM 1 expression. The specification teaches that in order to separate the fetal hepatic cell population from the hemopoietic cell population by ICAM-1 antibodies, then, in order to determine which fraction contains the hepatic cell populations, fractions can be sorted by FACS, and then screened by CFA (colony forming assay) for clonal growth potential. The specification teaches that the cells are defined by expression of albumin and alpha-fetoprotein and distinguishable morphologically. Sidescatter (SSC) was also used to separate the hepatic cells from hematopoietic cells. The specification further teaches that these cells are able to differentiate into the biliary cell linage in a culture system. See p. 24, Example #6.6. The specification teaches that specific cell surface and internal markers can be used to identify human hepatic precursor cells, including nonclassical MHC class I, alpha-fetoprotein, albumin and CK19 expression. See p. 27, Example #6.10 and #6.11.

State of the Art/Predictability of the Art. The specification teaches that a specific population of cells from rat fetal liver cells, those that are $RT1A^{1-}$, $OX18^{dull}$, ICAM-1^{+}, producing alpha-fetoprotein and albumin colonies are indicative of hepatic progenitor cells. See p. 21, lines 25-30. These cells are found have evidence for bipotentiality, as evidenced by the expression of CK19, which is a marker expressed by bile duct epithelial precursor cells. This provides evidence that the cells can differentiate to the biliary lineage in a culture system. See p. 24, Example #6.6.

The specification further provides teachings with regard to the isolation of human hepatic precursor cells by specific expression and lack of expression of particular markers. See p. 28-29, Example #6.11. Thus, it is clear from the teachings of the specification that particular marker expression, and lack of particular marker expression are critical to enable the claimed invention. The claims are not enabling because they are broadly directed to expression of particular markers (for example, MHC class Ib antigen, alpha-fetoprotein, albumin, CK19, or combinations thereof – claim 14) and some of the embodiments are broadly directed to cells that do not express MHC class Ia, and express ICAM (see claim1, for example). These claims are not found to be enabled by the instant invention because the recitation of these characteristics alone fails to attain the instant invention, which are bipotent hepatic progenitor cells. For example, the breadth of claim 1, which recites the expression of ICAM and lack of expression of MHC class Ia fails to be sufficient to enable isolated bipotent hepatic progenitor cells, because other cells (which are not bipotent hepatic progenitor cells) could be identified by these two markers. It is clear from the teachings of the specification that specific expression of markers identifies a population of bipotent hepatic progenitor. For example, the specification teaches that in rat fetal liver, MHC class I negative cells include hepatic bipotent progenitors, enucleated mature erythrocytes, and an unidentified cell population. See p. 10, lines 19-21. The specification teaches that hepatic cell populations that express ICAM-1 include hematopoietic, mesenchymal and mature

hepatic cells. Thus, the lack expression of MHC class I and expression of ICAM may not be sufficient to uniquely identify bipotent hepatic progenitor cells. Note further that MHC has three alleles, which are expressed throughout the population, thus, the lack of expression of class Ia may not, in itself, be sufficient to uniquely identify the bipotent hepatic progenitor cells.

The Amount of Experimentation Necessary. In view of the lack of teaching or guidance provided by the specification with regard to utilizing only particular markers to identify the bipotent hepatic progenitor cells, the teachings in the art to show that cells other than bipotent hepatic progenitor cells express the claimed markers, it would have required undue experimentation for one of skill in the art to practice the claimed invention.

Claims 1, 14, 27-55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that, "[A]pplicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now*

claimed." *Vas-Cath Inc. v. Mahurkar,* 19USPQ2d at 1117. The specification does not, "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

The claims are broadly drawn to isolated single-cell bipotent hepatic progenitors which express ICAM and do not express MHC class Ia, in further embodiments, the claims are directed to bipotent hepatic progenitors or their progeny, which express at least one MHC class Ib antigen, exhibit a numerically higher sidescatter value, express alpha-fetoprotein, albumin, CK19, or a combination thereof.

The claimed cells/compositions lack a written description because, as claimed, the expression of a particular marker (for example, ICAM, MHC class Ib, alpha-fetoprotein, albumin, CK19, or a combination thereof) and the lack of expression of a particular marker (for example, MHC class Ia) fails to describe single cell bipotent hepatic progenitor cells. Although the specification provides specific guidance with regard to the isolation of single cell bipotent hepatic progenitors, the claims, as written, fail to describe these cells, because the characteristics, as instantly claimed, fail to uniquely identify this cell population. There is no specific description of a cell with expression of ICAM and lack of MHC class Ia as a bipotent hepatic progenitor cell, such that one skilled in the art would recognize that Applicants had possession of the claimed invention. Although the specification describes methods of isolating the hepatic progenitor cells, the characteristics of the

cells require more than instantly claimed in order to describe the cells as hepatic progenitor cells.

The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described by the specification and which are not convention in the art at the time of filing. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that one of skill in the art would recognize that the inventor had possession of the claimed invention. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it.

See *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification only provided the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description of 35 U.S.C. 112 is severable from its enablement provision [see p. 1115].

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 14, 28, 42-49 are rejected under 35 U.S.C. 102(b) as being anticipated by Sargiacomo (cited in the prior Office action).

Although Applicants' amendments to the claims have overcome the prior rejection with regard to the recitation of bipotent hepatic progenitors, the claims, as instantly presented recite compositions that consist of bipotent hepatic progenitors and their progeny. Progeny of hepatic progenitor cells encompass hepatocytes, or other cells that are differentiated from the original progenitor cells. The specific properties that are recited in the claims are inherent properties to the cells. Because Sargiacomo teach cells isolated from human fetal livers, and the culture of these cells (see p. 481, 2nd column), they anticipate the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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